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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/908,992	07/19/2001	Joshua Syken	HMV-054.01	6851

25181 7590 01/15/2003

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EXAMINER

LI, QIAN J

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/15/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/908,992	SYKEN ET AL.
	Examiner Q. Janice Li	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 30 October 2002.

2a) This action is **FINAL**.                            2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) 9-20 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-8 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8.

4) Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.

5) Notice of Informal Patent Application (PTO-152)

6) Other: \_\_\_\_\_.

**DETAILED ACTION**

***Election/Restrictions***

Applicant's election with traverse of Group I, claims 1-8 in Paper No. 10, is acknowledged. The traversal is on the ground(s) that no undue burden would be required to search all groups. This is not found persuasive because it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent products (nucleic acids and proteins) and methods for *in vitro* protein production, and for *in vivo* and *ex vivo* gene/protein therapies. For example, the nucleic acid used in group IV is not required in group III, the consideration for *in vivo* use of the methods of groups III and IV is not required for that of group I, the pharmacokinetics and biodistribution is distinct for different agents used in the methods. The search and consideration for different products of groups II and I would have certain overlap, but they are not co-extensive. In view of the immense amount of literatures and databases currently available, it would require undue search and examination burden to the Office if all groups were examined together in this application. Therefore, it is maintained that these inventions are distinct due to their divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the separate classifications. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the

Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-20 are pending, however, claims 9-20 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-8 are under current examination.

***Priority***

This application claims the benefit of priority from U.S. provisional applications 60/219,718 and 60/219,537, filed on July 19 and July 20, 2000, respectively.

***Sequence Compliance***

The specification contains sequence disclosures (e.g. Figures 1B, 5, 6, 10) that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2) but are not present in the Sequence Listing and/or identified in the specification by sequence identifier numbers. Applicant must provide sequence identifiers for each sequence in the figures. In the case that certain sequences are not included in the original sequence submission, a paper copy and a computer readable copy of the Sequence Listing and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no

new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). A full response to this Office Action must include a complete response to the requirement for a Sequence Listing.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement*; Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

Claims 1, 3, and 5-7 are drawn to an isolated nucleic acid comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence set forth in SEQ ID No:3 or the complement thereof, which encodes a polypeptide having SEQ ID No: 9 (hTid-1s) or having about 1-20 conservative amino acid changes of SEQ ID No:9. Given the broadest reasonable interpretation, the claims embrace numerous nucleic acid sequences that are at least 90% identical to SEQ ID No: 3 in sequence identities. Considering the possible numbers of polypeptide variants coded by the nucleic acids, the art known knowledge is "EACH POSITION IN A PEPTIDE IS UNIQUELY DEFINED, THE NUMBER OF POSSIBLE PEPTIDES IS VERY LARGE, EVEN IN A RELATIVELY SHORT PEPTIDE. WHEN THE NUMBER OF AMINO ACID UNITS IN THE PEPTIDE CHAIN EQUALS  $N$ , THE NUMBER OF POSSIBLE PEPTIDES IS  $20^N$ ." (*Encyclopedia Britannica online*). Claim 4 is drawn to an isolated nucleic acid comprising SEQ ID No: 3. Given the broadest reasonable interpretation, the claim embrace numerous nucleic acids having any lengths as long as it comprises the SEQ ID No: 3. Although, one could make a polypeptide from the claimed nucleic acids, the specification fails to teach whether the polypeptide, the variants of Tid-1s, would function as hTid-1s.

The specification teaches that hTID1 is a human homolog of the *Drosophila* tumor suppressor l(2)tid, that the polypeptide SEQ ID No:9 (encoded by SEQ ID No: 3) is the short form of the two mitochondrial matrix localized splice polypeptide variants (hTid-1s), that both hTid-1L and hTid-1s retain their respective J domains. The specification goes on to teach that the expression of each of the two splice variants has opposing effects on a cell's ability to respond to an exogenous apoptotic stimulus, i.e.

enhancing or suppressing apoptosis triggered by both TNF and the DNA-damaging agent, respectively. Further, the J domain mutation of either Tid-1L or Tid-1s would reverse the supposed enhancing or suppressing effect.

It is noteworthy that the coding sequence of Tid-1L (SEQ ID No: 2) comprises the full length of SEQ ID No: 3, and the two sequences share >98% sequence homology, thus, it is crucial that the specification provides information on what amino acid residues are necessary and sufficient for enhancing or suppressing an apoptotic cellular activity. However, the specification provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in the encompassed polypeptides that would retain or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein hTid-1s. Since there are no example of a polynucleotide having at least 90% sequence identity with SEQ ID No: 3, and encodes a polypeptide function as that of SEQ ID No: 9, or a polypeptide known to have about 1-20 conservative amino acid changes of SEQ ID No: 9 and also have the desired function as SEQ ID No: 9, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Likewise, the specification fails to teach which of the mutants of the SEQ ID No: 9 could maintain the functional ability in promoting or suppressing the apoptotic response. For example, the coding sequence of hTid-1L (SEQ ID No: 2) meets the limitation of claim 1, i.e. having at least 90% sequence identity with SEQ ID No: 3, however, it has opposing effects of hTid-1s in the cellular apoptotic process. Therefore, from 90% sequence homology, one skilled in the

art could not predictably associate the polypeptide variants with the function of SEQ ID No: 9 encoded by SEQ ID No: 3. Therefore, the specification fails to provide an adequate written description commensurate with the scope of the claims.

The polynucleotides embraced by claim 2 must meet the following limitations, 1) an isolated nucleic acid comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence set forth in SEQ ID No:3 or the complement thereof, 2) wherein the complement hybridizes under stringent hybridization condition to SEQ ID No: 3, and 3) but not hybridizes to SEQ ID No: 2. Since SEQ ID No: 3 comprises 1362 base pairs, the length of the encompassed polynucleotides must be at least 1225 bps long; and because SEQ ID No: 3 shares 99% sequence identity with SEQ ID No: 2, it seems impossible to have a polynucleotide sequence that hybridizes to SEQ ID No: 3, but not SEQ ID No: 2. Therefore, the sequences encompassed by claim 2 have not been properly described.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the numerous nucleic acids comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence set forth in SEQ ID No: 3 and having the function of hTid-1s. Therefore, only the described SEQ ID No: 3 meets the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

As indicated *supra* in the written description section, the specification fails to provide an adequate description for the numerous nucleic acids comprising a nucleotide

sequence comprising SEQ ID No: 3 or which is at least 90% identical to the nucleotide sequence set forth in SEQ ID No:3 or the complement thereof. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed genus, SEQ ID No: 3 alone is insufficient to describe the genus, because it is unpredictable whether the polypeptide variants of SEQ ID No: 9 encoded by the claimed nucleic acids will function as hTid-1s.

In view of the state of the art in protein chemistry, it is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide-coding region determines amino acid sequence of the protein, it is the conformation of three-dimensional structures that allows the protein to function and carry out the messages of the genome. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach certain position in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). For example, Rap is a Ras-like GTPase localized mainly at endocytic and lysosomal vesicles, and has an effector domain virtually identical to that of Ras, however, Ras and Rap1 differ considerably in several aspects, Rap1 is considered to function as an antagonist of Ras signaling by trapping Ras effectors in an inactive complex (*Bos*, EMBO J 1998;17:6776-82, abstract). Interestingly, a single threonine residue change at position 61 contributes to the functional differences of Ras and Rap1; substitution of threonine for glutamine in Ras resulted in a strongly reduced intrinsic and GAP-induced GTPase activity (right column, page 6778). Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological

activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that for peptide hormones, which are comparable or smaller in size than the instant Tid-1s protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "CASE TO CASE PAINSTAKING EXPERIMENTAL STUDY" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active SEQ ID No: 9 with an amino acid sequence differing from SEQ ID NO: 9 since the amino acid sequence of such polypeptides could not be predicted. Likewise, when a polypeptide comprising the peptide (SEQ ID No: 9) encoded by SEQ ID No: 3, but the length of the polypeptide significantly surpasses SEQ ID No: 9, the folding and the function of the resulting polypeptide is also unpredictable.

In conclusion, one cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of active variants encompassed by these claims, thus would not know how to use the invention without first carrying out undue experimentation to determine which of the expression product of the nucleic acids would have the function of hTid-1s.

Accordingly, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is vague and indefinite because it recites, "the nucleotide sequence of SEQ ID No: 2, which encodes the carboxyl-terminal 33 amino acids of SEQ ID No:8" (lines 3-4). However, SEQ ID NO: 2 encodes the *full-length* amino acids of SEQ ID NO: 8, not just "the carboxyl-terminal 33 amino acids of SEQ ID No: 8". Thus, the metes and bounds of the claims are unclear.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-8 are rejected under 35 U.S.C. 102(b) as being anticipated by *Schilling et al* (Virol 1998;247:74-85, IDS/CB).

The claims are drawn to an isolated nucleic acid comprising a nucleotide sequence which is at least 90% identical to the nucleotide sequence set forth in SEQ ID No:3 or the complement thereof, which encodes a polypeptide having SEQ ID No:9; an isolated nucleic acid comprising SEQ ID No: 3, operably linked to a transcriptional control sequence, a vector or a host cell comprising the nucleic acids. Claim 8 is drawn to a method for producing the polypeptide encoded by SEQ ID No: 3 and its variants and complements by transfecting a cell with the nucleic acids.

*Schilling et al.* discloses a nucleic acid (hTid-1, AF061749 of GenEmb1 database) which shares 98.6% sequence identity with SEQ ID No: 3, and comprises 1340 bps of 1443 bps of SEQ ID No: 3, therefore, the complements of the nucleic acid would hybridize to SEQ ID No: 3. *Schilling et al.* also teaches that the nucleic acid encodes the hTid-1 protein (075472 in SPTREMBL-21 database), which contains 447 amino acids of SEQ ID No:9. Further, *Schilling et al.* teach using a plasmid containing full-length Tid-1 coding sequence operably linked to a promoter for in vitro production of Tid-1 protein (paragraph bridging left and right columns, page 83). Therefore, *Schilling et al.* anticipates the instant claims.

Claims 1, 3-8 are rejected under 35 U.S.C. 102(a) as being anticipated by *Skyen et al* (PNAS 1999 July 20;8499-8504, IDS/CD).

*Skyen et al.* teaches hTid-1s (SEQ ID No: 9) and its coding region (SEQ ID No: 3), cells (U20S) transfected with a plasmid vector comprising SEQ ID No: 3, operably linked to a transcriptional control sequence, and expressing hTid-1s (see Methods section on page 8499) with the plasmid vector. Therefore, *Skyen et al.* anticipates the instant claims.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li  
Examiner  
Art Unit 1632

QJL  
January 10, 2003

ANNE M. WEHBE PH.D  
PRIMARY EXAMINER

